An Evaluation of the Mutagenicity of Coke Oven Emissions Using the US EPA's 2005 Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens

Channa Keshava[1], Michael C. Cimino[2], Margaret Chu[1], Kerry L. Dearfield[3], Lynn Flowers[1], Nagalakshmi Keshava[1], Andrew D. Kligerman[4], Nancy E. McCarroll[2], Russell Owen[4], Resha M. Putzrath[1], Rita Schoeny[5]

[1]National Center for Environmental Assessment, Office of Research and Development, [2]Office of Prevention, Pesticides and Toxic Substances; [3]Office of Public Health Sciences, U.S. Department of Agriculture, Washington, DC; [4]National Health and Environmental Effects Research Laboratory, Research Triangle Park, NC; [5]Office of Water, U.S. Environmental Protection Agency, Washington, DC.

Introduction

- U.S. EPA recently released its revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) and Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens (U.S. EPA, 2005b)
- The guidance recommends the use of age-dependent adjustment factors for carcinogenic potency where there are no early-life studies, but where the weight of the evidence based on available information is sufficient to support a mutagenic mode of action for carcinogenesis
- U.S. EPA's Office of Air and Radiation, and Office of Research and Development utilized the Cancer Guidelines and Supplemental Guidance in the recently released Coke Oven Emissions Residual Risk Assessment to evaluate the risks associated with early-life exposure to coke oven emissions
- A review of the available mutagenicity data for coke oven emissions was performed to evaluate whether coke oven emissions may be carcinogenic through a mutagenic mode of action

Evaluation of Relevant Data on Mutagenicity of COE

A focused evaluation of the recent literature on the mutagenicity of coke oven emissions was performed. Selected relevant endpoints such as chromosomal damage, DNA adduct formation, genetic polymorphisms, and mutagenicity of urinary metabolites in coke oven workers are discussed in the following sections. The objective of this review was to evaluate key studies related to a mutagenic mode of action for carcinogenesis in response to coke oven emissions exposure.

Genetic/Chromosomal Damage in Coke Oven Workers

- Genetic/chromosomal damage has been observed in peripheral blood lymphocytes of exposed workers in humans exposed to coke oven emissions.
- In general, exposure to coke oven emissions induced sister chromatid exchanges (SCE) in the blood lymphocytes with the high frequency cell assay being more sensitive than SCE frequency.
- Statistically significant increases in chromosomal aberrations (CA) were found in several studies. In general, the cytokinesis blocked micronucleus assay (MN) and Comet assay showed positive responses. However, there are a few studies that showed either no increase in frequency of CA, MN, or SCE, or a decrease in MN frequency. The probable rationale for this disparity in results is that not all studies had similar concentrations or lengths of exposures. Some studies had subjects exposed to very high levels of coke oven emissions compared to other studies.

DNA Adduct Formation in Coke Oven Workers

- Coke oven emissions contain several PAHs such as benzo[a]pyrene, benz[a]-anthracene, benzo[b]fluoranthene, benzo[ghi]perylene, chrysene, and dibenz[ah]-anthracene. Several of the PAHs can be activated to metabolites which covalently bind to DNA forming stable adducts leading to DNA damage. Thus, the presence of measurable DNA adducts in workers exposed to coke oven emissions may be an indication of exposure and damage to DNA.
- Studies have shown significant increases in DNA adduct formation in lymphocytes and white blood cells of workers exposed to coke oven emissions compared to controls.
- There are a number of potential confounding factors associated with these studies, which may provide rationale for a lack of effects in some studies. Smoking status is a confounding factor that may play a significant role in PAH-DNA adduct formation; most studies, however, have controlled for smoker effect both in exposed and control groups. Inter-individual variations may also represent an important variability factor. These variations include, but are not limited to, fluctuating exposure levels and variations in metabolism and DNA repair.

Evaluation of Relevant Data on Mutagenicity of COE Contn.

Genetic Polymorphisms in Coke Oven Workers

- The role of gene polymorphisms in cancer from coke oven emissions has been investigated. The endpoints assayed include urinary mutagenicity, DNA adducts, and MN formation. In general, glutathione S-transferase M1 (*GSTM1),* N-acetyl transferase (*NAT),* glutathione S-transferase T1 (*GSTT1),* and epoxide hydrolase (*mEH)* genes have been analyzed.
- Several studies have included internal measures of PAH exposure or environmental measurements of PAH exposure. Most of the investigations include well-controlled assays for polymorphisms.
- Overall, these studies provide moderate support for an association between genotoxicity-related endpoints and metabolic enzymes such as *GSTM1, GSTT1, GSTP1, NQO1, NAT2* and *mEH*. The investigations indicate that coke oven emissions to be carcinogenic by a mutagenic mode of action.

Mutagenicity of Urinary Metabolites in Coke Oven Workers

- Urinary mutagenicity testing has been used in the biological monitoring of exposure to mutagenic/carcinogenic agents. The advantages of urinary markers are their non-invasiveness and ready accessibility.
- The urinary excretion of 1-hydroxypyrene, a metabolite of pyrene, has been used as a biological indicator of exposure to PAHs in several occupational and environmental studies. The measurement of urinary mutagenicity by the Ames assay has been used to detect absorption of potentially mutagenic compounds as a non-specific biological marker of exposure. It has been used together with 1-hydroxypyrene determination to assess the exposure of coke oven workers to genotoxicants.
- Several studies have assessed the presence of mutagens in the urine of exposed populations and have reported increased urinary mutagenic activity in PAH-exposed workers.
- The above studies show an association between mutagenic responses from worker urine samples and urinary PAH markers following exposure to coke oven emissions. It should be noted, however, that there are studies in which urinary markers did not correlate with any cytogenetic damage.

Conclusions

- The overall weight of evidence upon review of a substantial body of data, we conclude that coke oven emissions are expected to cause cancer through a mutagenic mode of action, although other modes of action are not precluded.
- This conclusion is based on observation of mutagenic and other genotoxic effects after both *in vitro* and *in vivo* exposure to coke oven emissions in human and other mammalian cells, as well as other test organisms.
- In addition, there is a voluminous body of literature demonstrating the mutagenicity of coke oven emission components, including PAHs and heterocyclic amines.
- Therefore, the use of ADAFs for early-life exposure to coke oven emissions is warranted.

References and Disclaimer

- U.S. EPA. (2005a) Guidelines for carcinogen risk assessment. EPA/630/P-03/001F. www.epa.gov/cancerguidelines
- U.S. EPA. (2005b) Supplemental guidance for assessing cancer susceptibility from early-life exposure to carcinogens. EPA/630/R-03/003F. http://www.epa.gov/cancerguidelines
- (**Disclaimer:** The views expressed in this abstract are those of the authors and do not represent the policy of either the U.S. Environmental Protection Agency or the U.S. Department of Agriculture)